cell is obtained by introducing into a similar host cell a second genetic vector essentially identical to said first genetic vector except that it does not bear said gene insert.

83. (New) The method of Claim 80 wherein examination for the graded cellular response to the chemical agent includes comparing the response of said treated cell to the response of a comparable untreated cell.

84. (New) The method of Claim 80 wherein examination includes comparing the graded cellular response of said treated test cell to that of a comparably treated test cell which does not overproduce the selected protein.

85. (New) The method of Claim 80 wherein examination includes comparing the graded cellular response of said test cell to the chemical agent with the phenotypic response of a second test cell to a known inhibitor or activator of the protein.

86. (New) The method of any one of Claims 52 to 57 and 80 to 85 wherein the chemical agent directly interacts intracellularly with the protein.

Remarks

Claims 33-58 were examined. In response, Applicant has amended Claims 48 and 57 to provide proper antecedent basis. Claims 35, 41 and 51 have been canceled and submitted in independent form. Claims 36, 37, 38, 42 and 58 have been amended to eliminate dependencies which are duplicative of newly added independent claims that incorporate dependent claims to which objection was made. Complete continuation data and an abstract have been provided. Favorable reconsideration and allowance of the application is respectfully requested.

Claims 59-86 are new. The Examiner indicated that Claims 35, 38, 41-42, 51 and 58 would be allowable in independent form. Accordingly, independent Claims 59, 63, 67, 69, 71 and 80 are added. New Claim 59 combines independent Claim 33 and Claims 34-35.

New Claim 63 combines independent Claim 33 and Claim 38. New Claim 67 combines independent Claim 39 and Claims 40-41. New Claim 69 combines independent Claim 39 and Claim 42. New Claim 71 combines independent Claim 43 and Claim 51. New Claim 80 combines independent Claim 52 and Claim 58.

Claims 59 and 67 incorporate introducing a gene encoding the enzyme into a host cell by means of a genetic vector. Claims 63, 69, 71 and 80 incorporate the claim element "graded cellular response" as provided at Page 12, lines 22-28 of the Specification.

New dependent Claims 60-62, 72-78 and 81-85 further limit their respective independent claims in the manner of preexisting dependent Claims 36-38, 44-50 and 53-57. New dependent Claims 64, 65 and 68 further limit their respective independent claims with elements which are commonly recited herein, e.g., in preexisting Claims 36, 37, and 38.

New dependent Claims 66, 70, 79 and 86 recite intracellular interaction between a chemical agent and a protein or enzyme. Support for these claims is found both in the Specification and in Applicant's U.S. Patent No. 4,980,281 ("'281 patent") which is the basis for priority of this application. For example, at Page 13, lines 21-30 ('281 patent, Col. 6, ll. 45-54), identification of inhibitors or activators of wholly intracellular enzymes (protein kinase C, ornithine decarboxylase, cyclic AMP-dependent protein kinase, c-src and c-ras) and enzymes with intracellular domains of interest (protein kinase domains of the insulin and EGF receptors) is disclosed. At Page 14, Lines 11-16 ('281 patent, Col. 6, ll. 63-68), it is disclosed that PKC has been shown to phosphorylate several intracellular protein substrates, including EGF-R, $pp60^{src}$, the insulin receptor, $p21^{ras}$ and many others. At Page 23, lines 1-3 ('281 patent, Col. 10, ll. 24-26) the application of principles of the invention is exemplified by a "system useful for screening for potent inhibitors of protein kinase C (PKC), a high-affinity *intracellular receptor* for tumor-promoting agents."

Claims 33-34, 36-37, 39-40, 43-50 and 52-57 have been rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a), as obvious over Williams et al. (U.S. Pat. No. 6,043,211) or Escobedo et al. (U.S. Pat. No. 6,110,737). It is noted that the aforementioned patents claim priority back to a common first application, U.S. Ser. No. 07/151,414 ("Williams"), with substantial new matter present in subsequent applications and consequently in the cited patents. Only the subject matter of the first application is prior art under § 102(e) to this application. Therefore, we address only that common subject matter below as "Williams."

The instant claims are directed to screening for inhibitors or activators of the overexpressed protein of interest, while Williams is directed to screening for agonists or antagonists of the ligand.

The Examiner has pointed to the section at page 47-48 entitled "Screening Assay to Detect Activators and Inhibitors of the Insulin Receptor" and the sentence at page 18, lines 24-28 as the basis of the Examiner's position that Williams' test system appears to be within the scope of Applicant's claims. Applicant believes that these portions of the Specification do not support such an interpretation.

In the identified portions of the specification, Applicant uses the terms "insulin agonist/antagonist" and "insulin receptor agonist/antagonist" indistinguishably, but it is evident that the Applicant is referring to agonists and antagonists of the insulin receptor. The section pointed out by the Examiner at pages 47 to 48 is specifically entitled "Screening Assay to Detect Activators and Inhibitors of the Insulin *Receptor*," and concludes "[m]ost importantly, this insulin *receptor* assay system demonstrates yet another direct application of the utility of stable overproduction of a protein-of-interest (POI) for the development of powerful assay systems capable of detecting activators or inhibitors of any POI." (page 48, lines 17-22). The POI that is overproduced is the insulin receptor, *not* insulin. The test cell is

used to detect activators or inhibitors of the insulin receptor, *not* insulin. Although insulin receptor agonists and antagonists are alternately referred to as "insulin agonists" or "insulin antagonists," Applicant believes that one of ordinary skill in the art would correctly understand the terms "insulin agonist/antagonist" as referring in context to "insulin receptor agonist/antagonist."

The Examiner has noted the apparent disjunction between the heading at Page 47, lines 11-12, referring to "Activators and Inhibitors of the Insulin Receptor" and the following paragraph which discusses screening for "insulin agonists and antagonists." (Page 47, lines 17-19). However, other passages under the subheading referred to by the Examiner support the Applicant's interpretation, as do numerous other sections of the specification where other POIs have been disclosed, most notably PKC. The following paragraph (Page 47, Lines 21-27) discloses an assay whereby test compounds are applied to cells and wherein no ligand is specified. Two paragraphs later (Page 48, Lines 3-10), reference is made to agents which are "insulin agonists." These are compounds screened for their ability to "mimic the effects of insulin," and thus are agonists of the insulin receptor and not of insulin itself.

Moreover, this is consistent with the entire body of the specification which is exclusively directed to inhibitors or activators of the protein of interest, which in this case is clearly and expressly the insulin receptor, not insulin. In Example 5, starting at Page 44, Line 11, Applicant expressly teaches studies designed to test the utility of his invention with the human insulin receptor as the POI, i.e., as the protein which is overproduced, and which test system is therefore capable of detecting agonists and antagonists of insulin action, that is, compounds which, like insulin, bind directly to, and therefore inhibit or activate the insulin receptor.

Applicant further notes that the passage at Page 48, Lines 3-10, cited above for its reference to "agents which are insulin agonists," specifically refers back to the "methods

described above for PKC" which relate to test cell lines containing PKC as the protein of interest. Applicant's methods for using a PKC test cell line are described as relating to inhibitors and activators of PKC, not to inhibitors or activators of *ligands* of PKC. The use of this test system is described as resulting in "a novel cellular phenotype(s) (in this case anchorage independence) which can be directly modulated by chemical agents which interact with the protein." (Page 39, Lines 16-26). Moreover, the "cell lines which resulted from the application of this method are highly sensitive and responsive both to agents which activate PKC as well as those which inhibit PKC." (Page 23, Lines 3-6).

Lastly, Applicant wishes to point out that elsewhere in his specification, in similar circumstances, he has sometimes used the designation of "agonist" and "antagonist" noted by the Examiner, although the intent is apparent. For example, at Page 48, Lines 24-34 of the Specification, Applicant discusses the findings of Julius et al. (1989) Science 244:1057-1062, which is of record. At Lines 29-30 of Applicant's Specification, mesulergine is stated to be a serotonin antagonist. As is known in the art, and as is apparent from Figure 3 of Julius, mesulergine actually exerts its inhibitory activity by binding to the serotonin receptor 5HT1c.

Unlike Williams, Applicant submits that the instant claims are directed to screening for substances which directly inhibit or activate the POI, and not its ligand, nor any other proteins acting upstream or downstream of the POI which mediate the functioning of the POI in the cell. Accordingly, Applicant's claims are not and cannot be anticipated by the methods of Williams since the Williams methods are directed to screening for agonists or antagonists of a particular ligand, PDGF.

Furthermore, Applicant respectfully submits that the instant claims are not obvious in view of Williams.

First, as the Examiner appreciates, Williams provides cells transfected with a cDNA encoding a human platelet-derived growth factor (PDGF) receptor (hPDGF-R). Once the

hPDGF-R is introduced into these cells, the authors demonstrate that treatment of the cells with PDGF induces cellular responses typical of a mitogenic growth factor, including increased DNA synthesis and phosphorylation of tyrosine residues on proteins which interact with the PDGF receptor to mediate the growth inducing effects of PDGF.

William explains, at most, that "the construct can be used for enhancing PDGF response of cells, determining the regions involved in transducing the signal in response to PDGF binding, providing mutated analogs and evaluating drugs for their physiological activity." However, Williams does *not* teach the underlying molecular mechanism through which said drug-induced "physiological activity" is manifest. More specifically, Williams does *not* teach that when the test system is subjected to exogenous substances and a phenotypic change occurs, it is due to an inhibitor or activator of PDGF-R. Furthermore, as is disclosed in the *later* Williams et al. reference, such phenotypic changes may be due to interaction between a test substance and numerous target proteins which mediate the PDGF-induced signal transduction cascade in cells. These include, at a minimum, PDGF itself, the PDGF receptor, PI-3 Kinase (a downstream target protein which interacts with the PDGF-R, and other proteins downstream of both the PDGF-R and PI-3 Kinase (PLC-gamma, c-raf-1, PKC, and others). Thus, Williams et al. actually teaches *away* from using the system to identify inhibitors or activators specifically of the PDGF receptor produced by the cell. There is no suggestion to provide an assay system capable of identifying substances that act specifically on the PDGF receptor by utilizing a responsive change in a phenotypic characteristic of the cell which is evoked by the production of the POI in the cell, as taught by the Applicant.

Furthermore, as a result of the lack of suggestion to provide such a target protein specific assay system, Williams would not enable one of ordinary skill to distinguish among substances which act on the ligand (PDGF), which act on the protein-of-interest (PDGF-R),

and which act on any other protein (PI-3 Kinase, PLC-gamma, c-raf-1, PKC, and others) which has a function at any point along the pathway from receptor activation or inhibition to display of the phenotype which is being observed.

For these and other reasons, Applicant believes that all of the rejected claims are patentable over Williams and Escobedo. In addition, Applicant urges that the dependent claims are separately patentable, as the Examiner has acknowledged with respect to claims 35, 38, 41-42, 51 and 58.

It is believed that the amendment fully responds to the Examiner's rejection and allowance of the claims is respectfully requested.

Respectfully submitted,

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